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10/607,583	06/25/2003	Kai Y. Xu	A9422	5808

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SKELDING, ZACHARY S

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1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/607,583	XU, KAI Y.	
	Examiner	Art Unit	
	Zachary Skelding	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2007 and 07 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *8-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8-25-03*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *5-7-07*.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election, without traverse, filed February 20, 2007, is acknowledged.

   Claims 1-47 are pending.

2. Applicant's election, without traverse, of Group I, drawn to anti-SEQ ID NO: 1 antibodies, encompassing claims 1-8 and 11-14 is acknowledged.

   However, upon reconsideration by the Examiner, it was determined that due to an inadvertent error the Groups set forth in the Restriction Requirement of September 21, 2006 were not as they should be. Thus, the Restriction Requirement of September 21, 2006 was **VACATED** and the following new restriction requirement is set forth:

Restriction Requirement

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-7, drawn to an **antibody that** binds an amino acid sequence comprising **SEQ ID NO: 1**, or an isoform thereof, classified in Class 530, subclass 387.1.

II. Claims 8-14, drawn to an **antibody that** binds an amino acid sequence comprising **SEQ ID NO: 2**, or an isoform thereof, classified in Class 530, subclass 388.1.

III. Claims 15 and 16 drawn to **a peptide comprising SEQ ID NO: 1**, and derivatives or isoforms thereof, classified in Class 530, subclass 300.

IV. Claims 17-23, drawn to **polynucleotide** encoding an amino acid sequence comprising **SEQ ID NO: 1,** or isoforms thereof, and vectors comprising said sequence, classified in Class 536, subclass 23.5 and Class 435, subclass 320.1.

V. Claims 24 and 25, drawn to **a peptide comprising SEQ ID NO: 2**, and derivatives or isoforms thereof, classified in Class 530, subclass 326.

VI. Claims 26-32 drawn to a **polynucleotide** encoding an amino acid sequence comprising **SEQ ID NO: 2,** or isoforms thereof, and vectors comprising said sequence, classified in Class 536, subclass 23.2 and Class 435, subclass 320.1.

VII. Claims 33-41, drawn to **method of making antibody to an ATPase**, classified in Class 435, subclass 70.1.

VIII. Claims 42 and 43, drawn to a **method of diagnosis**, classified in Class 435, subclass 7.1.

IX. Claims 44-45, drawn to a **method for targeting and blocking the SEQ ID NO: 1 site of an ATPase to identify molecules useful for therapy of patients susceptible to heart disease,** classified in Class 435, subclass 183.

X. Claims 46-47, drawn to a **method for targeting and blocking the SEQ ID NO: 2 site of an ATPase identify molecules useful for therapy of patients susceptible to heart disease,** classified in Class 435, subclass 196.

3. Groups I-VI are different products. The products are patentably distinct because their structures, physicochemical properties and/or mode of action are different, and they do not share a common structure that is disclosed to be essential for common utility.

   Furthermore, a search of these products would require a non-coextensive search of the scientific literature. Therefore, each product is patentably distinct, and searching these inventions together would impose an undue burden.

4. Groups VII-X are different methods, which differ with respect to one or more ingredients, method steps, and/or endpoints; therefore, each method is patentably distinct. Further, the distinct ingredients, method steps, and/or endpoints require separate and distinct searches.

5. These inventions are distinct for the reasons given above. In addition, they have acquired a separate status in the art as shown by different classification and/or recognized divergent subject matter. Further, even though in some cases the classification is shared, a different field of search would be required based upon the structurally distinct products recited and the various methods of use comprising distinct method steps. Moreover, a prior art search also requires a literature search.

   In addition, due to the size of the biological sequence databases, it takes significant time to search any given sequence. Moreover, it is additionally burdensome to search more than one structurally distinct biological sequence because patent applicants and prior art references often describe a biological sequences in different ways, and undue burden is required to correlate more than one biological sequence with the biological sequences as defined in the prior art. See the Official Gazette Notice of March 27, 2007 (Week #13).

   Thus it would be an undue burden for the examiner to search more than one structurally distinct invention. Accordingly, restriction for examination purposes as indicated is proper.

6. During a telephone conversation with applicant's representative of record, Dr. Todd Buck, on May 7, 2007 a provisional election, without traverse, was made to prosecute the invention of Group I, claims 1-7 (interview summary attached). Affirmation of this election must be made by applicant in replying to this Office action.

   Thus, claims 1-7 are under examination as they read on an antibody which recognizes the amino acid sequence comprising SEQ ID NO: 1.

Accordingly, claims 8-47 are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being directed to a non-elected invention.

7. The claims under examination appear to be entitled to the benefit of priority of USSN 60/391,514, filed October 18, 2002, ***except*** for claim 9, which recites that the claimed antibody "increases myocyte intracellular diastolic and systolic calcium" and appears to be adequately supported under 35 U.S.C. § 112, 1st paragraph only as of the filing of the instant application, June 25, 2003.

8. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

   The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

9. 35 U.S.C. 101 reads as follows:

   > Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

10. **Claim 1-4 are rejected under 35 USC § 101** because the claimed invention is directed to non-statutory subject matter, a product of nature.

    The instant claims are drawn to an antibody or polyclonal antibodies which recognize(s) an amino acid sequence comprising SEQ ID NO: 1.

    However the instant claims, as written, do not sufficiently distinguish over naturally occurring antibodies that bind an amino acid sequence comprising SEQ ID NO: 1 as it occurs in a mouse or rat because the claims do not particularly point out any non-naturally occurring differences between the claimed antibodies and naturally occurring antibodies. In the absence of the hand of man, naturally occurring antibodies are considered non-statutory subject matter. See Diamond v. Chakrabarty, 447 U.S. 303, 206 USPQ 193 (1980).

    Applicant must amend the instant claims to indicate the hand of man and point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

    > The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. **Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph,** as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, and dependent claims thereof, are indefinite in the recitation of "an antibody that recognizes the amino acid sequence comprising RSATEEEPPNDD (SEQ ID NO: 1) of the α-subunit of Na^++K^+-ATPase, or an isoform of the amino acid sequence."

It is not clear if the recitation, "an isoform of the amino acid sequence" in claim 1 refers to an "isoform" of ***the amino acid sequence comprising*** SEQ ID NO: 1 **OR** an ***"isoform" consisting of SEQ ID NO: 1 itself,*** which further comprises amino acid sequence. Thus, the metes and bounds of claim 1, and dependent claims thereof, are not clear.

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. **Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph,** as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1, and dependent claims thereof, recite "an antibody that recognizes the amino acid sequence comprising RSATEEEPPNDD (SEQ ID NO: 1) of the α-subunit of Na^++K^+-ATPase, or an isoform of the amino acid sequence."

While it is not clear exactly what is meant by the recitation, "an isoform of the amino acid sequence" in claim 1 (see rejection under 35 U.S.C. § 112, 2nd paragraph above), for the purposes of examination under 35 U.S.C. § 112, 1st paragraph, "an isoform of the amino acid sequence" in claim 1 will be read as if it refers to an ***"isoform" of SEQ ID NO: 1 itself,*** which is defined in the instant specification. In particular, according to the instant specification, an isoform of SEQ ID NO: 1 differs in sequence from SEQ ID NO: 1 by 1-10 amino acids (see, for example, page 7, 3rd paragraph).

Therefore, the instant claims, given their broadest reasonable interpretation consistent with the instant specification, read on everything from antibodies that bind an amino acid sequence comprising SEQ ID NO: 1 to antibodies that bind an amino acid sequence comprising a sequence 83% different from SEQ ID NO: 1.

For example, one "isoform" of SEQ ID NO: 1 is the homologous sequence from human α1 Na^++K^+-ATPase which differs from SEQ ID NO: 1 at four residues: **QA**ATEEEP**Q**ND**N**; however, it is important to note that overall the human and rat α1 Na^++K^+-ATPase are 96% identical across their full length 1023 amino acids (see attached alignment between rat_NaK vs. human_NaK).

However, it is highly unpredictable that an antibody which binds a polypeptide comprising an isoform of SEQ ID NO: 1 that differs by as many as 10 of 12 amino acids of SEQ ID NO: 1 would also bind, for example, a polypeptide comprising SEQ ID NO: 1 or a polypeptide highly similar to a polypeptide comprising SEQ ID NO: 1, such as the rat/mouse/human α1 Na^++K^+-ATPases, especially in light of the basic prinicipals of antigen-antibody binding as discussed in Janeway et al. (Immunobiology, 5th Ed., Garland Science, pp. 100-105 (2001).

Moreover, the instant specification does not provide sufficient direction or guidance to use antibodies that bind an isoform of SEQ ID NO: 1 but do ***not*** bind rat/mouse/human Na^++K^+-ATPase because, according to the instant specification, the antibodies of the present invention are useful as diagnostic agents to detect human Na^++K^+-ATPase, or to treat human cardiac conditions (see, for example, page 5, 1st to 3rd paragraphs and page 23, 1st-2nd paragraphs).

Accordingly, the instant specification does not provide sufficient direction or guidance to make and use antibodies encompassed by the breadth of the instant claims.

Thus, the instant claims encompass in their breadth antibodies to a multitude of polypeptide isoforms, for which it is difficult to predict which isoforms will result in an antigen that will generate an antibody that will, in turn, bind a different protein, i.e., a polypeptide comprising SEQ ID NO: 1 or a polypeptide highly similar to a polypeptide comprising SEQ ID NO: 1.

Without sufficient guidance or direction for which amino acid sequences and which mutation(s) can be tolerated in the structures of these protein, while still retaining the immunogenicity necessary to generate an antibody that will recognize a polypeptide comprising SEQ ID NO: 1, or a polypeptide highly similar to a polypeptide comprising SEQ ID NO: 1, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

16. **Claims 1-7 are rejected under 35 U.S.C. 102(e)** as being anticipated by Rosen et al., (US 20030054421) as evidenced by Bost et al. (Immunol. Invest. 1988; 17:577-586) and Bendayan et al. (J. Histochem. Cytochem. 1995; 43:881-886) and the instant specification at page 3, 3rd paragraph and page 43-44 (see entire document for each).

Rosen teaches SEQ ID NO: 745 (see US 20030054421 on http://seqdata.uspto.gov, the Publication Site for Issued and Published Sequences (PSIPS) and MPEP § 2434) which is 94% identical across residues 1-707 of the Rat NaK ATPase sequence obtained from Genbank accession number AAA416781 wherein the Rat Genbank sequence comprises SEQ ID NO: 1 of the instant application (see attached alignment, SEQ ID NO: 1 of the instant application is marked).

Rosen further teaches antigenic epitopes of SEQ ID NO: 745, such as the epitope comprising residues 158-TEEEPQNDN-166 of SEQ ID NO: 745 (see, in particular, page 75, row 12), which is identical to claimed SEQ ID NO: 1, but for two mismatches. Rosen teaches that antibodies can be generated against SEQ ID NO: 745, per se, or an antigenic epitope of SEQ ID NO: 745, for example, the epitope comprising residues 158-TEEEPQNDN-166 of SEQ ID NO: 745 (see, for example, pages 76-77, paragraphs [0106]-[0111] and page 82, paragraph [0158]).

Rosen further teaches that the antibodies that bind SEQ ID NO: 745, or an antigenic epitope thereof, can be polyclonal, monoclonal or humanized (see, for example, pages 82-86, paragraphs [0158]-[0180]).

Rosen further teaches that for in vivo diagnostic use and treatment, for example, to detect the overexpression of SEQ ID NO: 745 in breast and/or ovarian cancer, humanized antibodies are preferable (see, for example, page 5, paragraph [0042], pages 104-105, paragraphs [0337]-[0346], including paragraph [0338]).

As evidenced by Bost, antibodies can be specific for a given epitope and cross-reactive with multiple antigens. For example, Bost teaches antibodies which cross-react with IL-2 and HIV envelope protein, and establish that the binding to each protein is due to the presence of a homologous sequence in each protein of six amino acids, four of which are identical (see entire document, in particular the Abstract and Discussion, pages 577 and 583-585). Antibodies which bound either the HIV or IL-2 derived sequence did not cross-react with irrelevant peptides (see, in particular Results, pages 579-583).

As further evidenced by Bendayan et al., a monoclonal antibody can be highly specific for a given epitope and cross-reactive with antigens from different species or even distinct proteins not related to the original antigen (See entire document, in particular Discussion, pages 886-887).

Given the antibodies of Rosen, which are raised against a polypeptide having an amino acid sequence nearly identical to SEQ ID NO: 1 of the instant claims, and given that antibodies can be both specific and cross-reactive with antigens from different species (or even distinct proteins not related to the original antigen) as evidenced by Bost and Bendayan, the antibodies of Rosen would inherently bind SEQ ID NO: 1.

Moreover, given that antibodies which bind to SEQ ID NO: 1 inherently have the particular biological properties recited in the claims 2 and 3 when binding to the α subunit of rat Na^++K^+-ATPase as evidenced by the instant specification at page 3, 3rd paragraph and page 43-44. the antibodies of Rosen would inherently possess the properties recited in claims 2 and 3 upon binding to rat Na^++K^+-ATPase.

Moreover, it is noted that claim 7 recites, "the antibody of claim 1, wherein the antibody is administered to a patient...suffering from or susceptible to heart disease and/or muscle contractile disorders," which, given its broadest reasonable interpretation consistent with the instant specification, reads on administration to most of the industrialized world since most of the industrialized world is susceptible to heart disease as it is the most frequent cause of death in the industrialized world. Moreover, the "wherein..." recitation in claim 7 is an intended use of the claimed antibody, and if the prior art structure is capable of performing the intended use, then it meets the claim. In re Casey , 152 USPQ 235 (CCPA 1967); In re Otto, 136 USPQ 458, 459 (CCPA 1963).

Therefore, the teachings of Rosen, as evidenced by Bost, Bendayan and the instant specification, anticipate the instant claims.

Since the Office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibodies do not bind a polypeptide comprising SEQ ID NO: 1. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); *In re Fitzgerald* et al., 205 USPQ 594 (CCPA 1980).

17. **Claims 1, 4 and 7 are rejected under 35 U.S.C. 102(b)** as anticipated by Ball et al. (Biochim Biophys Acta. 1987 Nov 5;916(1):100-11, of record) as evidenced by Bost et al. (Immunol. Invest. 1988; 17:577-586) and Bendayan et al. (J. Histochem. Cytochem. 1995; 43:881-886)(see entire document for each).

Ball teaches a polyclonal antibody raised against the peptide **EA**ATEEEP**Q**ND**N** (see, in particular, page 102, Fgiure 1), wherein the residues that are different between the peptide of Ball and SEQ ID NO: 1 are highlighted. Ball further shows that these anti-peptide antibodies bind not only the peptide, but also the peptide in the context of denatured lamb kidney Na^++K^+-ATPase (see, in particular, page 104, right column).

As evidenced by Bost, antibodies can be specific for a given epitope and cross-reactive with multiple antigens. For example, Bost teaches antibodies which cross-react with IL-2 and HIV envelope protein, and establish that the binding to each protein is due to the presence of a homologous sequence in each protein of six amino acids, four of which are identical (see entire document, in particular the Abstract and Discussion, pages 577 and 583-585). Antibodies which bound either the HIV or IL-2 derived sequence did not cross-react with irrelevant peptides (see, in particular Results, pages 579-583).

As further evidenced by Bendayan et al., a monoclonal antibody can be highly specific for a given epitope and cross-reactive with antigens from different species or even distinct proteins not related to the original antigen (See entire document, in particular Discussion, pages 886-887).

Given the antibodies of Ball, which are raised against a peptide sequence having substantial overlap with SEQ ID NO: 1 of the instant claims, and given that antibodies can be both specific and cross-reactive with antigens from different species (or even distinct proteins not related to the original antigen) as evidenced by Bost and Bendayan, the antibodies of Ball would inherently bind SEQ ID NO: 1.

Therefore, the teachings of Ball, as evidenced by Bost and Bendayan anticipate the instant claims.

Since the Office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibodies do not bind a polypeptide comprising SEQ ID NO: 1. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); *In re Fitzgerald* et al., 205 USPQ 594 (CCPA 1980).

Moreover, it is noted that claim 7 recites, "the antibody of claim 1, wherein the antibody is administered to a patient...suffering from or susceptible to heart disease and/or muscle contractile disorders," which, given its broadest reasonable interpretation consistent with the instant specification, reads on administration to most of the industrialized world since most of the industrialized world is susceptible to heart disease as it is the most frequent cause of death in the industrialized world. Moreover, the "wherein..." recitation in claim 7 is an

intended use of the claimed antibody, and if the prior art structure is capable of performing the intended use, then it meets the claim. In re Casey , 152 USPQ 235 (CCPA 1967); In re Otto, 136 USPQ 458, 459 (CCPA 1963).

18. **Claims 1-3, 5 and 7 are rejected under 35 U.S.C. 102(b)** as anticipated by Arystarkhova et al., (J Biol Chem. 1992 Jul 5;267(19):13694-701) as evidenced by Bost et al. (Immunol. Invest. 1988; 17:577-586) and Bendayan et al. (J. Histochem. Cytochem. 1995; 43:881-886) and the instant specification at page 3, 3rd paragraph and page 43-44 (see entire document for each).

Arystarkhova teaches a monoclonal antibody, "Vg4", which binds, at the very least, residues QAATEEEPQNDNL of human α1 Na^++K^+-ATPase, in particular residues EEEP which are conserved between both rat and human α1 Na^++K^+-ATPase (see Arystarkhova et al., J Biol Chem. 1992 Jul 5;267(19):13694-701, Discussion pages 13700-13701, in particular paragraph bridging columns on page 13700).

As evidenced by Bost, antibodies can be specific for a given epitope and cross-reactive with multiple antigens. For example, Bost teaches antibodies which cross-react with IL-2 and HIV envelope protein, and establish that the binding to each protein is due to the presence of a homologous sequence in each protein of six amino acids, four of which are identical (see entire document, in particular the Abstract and Discussion, pages 577 and 583-585). Antibodies which bound either the HIV or IL-2 derived sequence did not cross-react with irrelevant peptides (see, in particular Results, pages 579-583).

As further evidenced by Bendayan et al., a monoclonal antibody can be highly specific for a given epitope and cross-reactive with antigens from different species or even distinct proteins not related to the original antigen (See entire document, in particular Discussion, pages 886-887).

Given that antibodies can be both specific and cross-reactive with antigens from different species (or even distinct proteins not related to the original antigen) as evidenced by Bost and Bendayan, and further given the extensive homology between rat and human polypeptides (96% identity across 1023 amino acids, see attached alignment between rat_NaK and human_NaK), indicating an overall conservation of structure, and further given that the residues to which the reference antibody binds, in particular residues EEEP which are critical for Vg4 binding, are conserved between rat and human, the reference antibody would bind to the claimed sequence.

Moreover, given that antibodies which bind to SEQ ID NO: 1 inherently have the particular biological properties recited in the claims 2 and 3 when binding to the α subunit of rat Na^++K^+-ATPase as evidenced by the instant specification at page 3, 3rd paragraph and page 43-44, the antibodies of Arystarkhova would inherently possess the properties recited in claims 2 and 3 upon binding to rat Na^++K^+-ATPase.

Therefore, the teachings of Arystarkhova,, as evidenced by Bost, Bendayan and the instant specification, anticipate the instant claims.

Since the Office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibodies do not bind a polypeptide comprising SEQ ID NO: 1. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); *In re Fitzgerald* et al., 205 USPQ 594 (CCPA 1980).

Moreover, it is noted that claim 7 recites, "the antibody of claim 1, wherein the antibody is administered to a patient...suffering from or susceptible to heart disease and/or muscle contractile disorders," which, given its broadest reasonable interpretation consistent with the instant specification, reads on administration to most of the industrialized world since most of the industrialized world is susceptible to heart disease as it is the most frequent cause of death in the industrialized world. Moreover, the "wherein..." recitation in claim 7 is an intended use of the claimed antibody, and if the prior art structure is capable of performing the intended use, then it meets the claim. In re Casey , 152 USPQ 235 (CCPA 1967); In re Otto, 136 USPQ 458, 459 (CCPA 1963).

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. **Claims 1-3 and 5-7 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Arystarkhova et al., (J Biol Chem. 1992 Jul 5;267(19):13694-701) in view of Rosen et al. (US 20030054421), Schwinger et al. (Circulation. 1999 Apr 27;99(16):2105-12), Mohraz et al. (J Biol Chem. 1994 Jan 28;269(4):2929-36, or record), Bost et al. (Immunol. Invest. 1988; 17:577-586), Bendayan et al. (J. Histochem. Cytochem. 1995; 43:881-886) and the instant specification at page 3, 3rd paragraph and page 43-44, and (see entire document for each).

The teachings of Arystarkhova, Bost, Bendayan and the instant specification are given in the previous section.

The claimed invention differs from these teachings in the recitation of the humanized antibodies.

However, Rosen teaches that for in vivo diagnostic use and treatment, for example to detect the overexpression of SEQ ID NO: 745 in breast and/or ovarian cancer, humanized antibodies are preferable (see, for example, page 5, paragraph [0042], pages 104-105, paragraphs [0337]-[0346], including paragraph [0338]).

While Arystarkhova is not concerned with the α1 Na^++K^+-ATPase expressed in breast and/or ovarian cancer cells, Arystarkhova is concerned with the α1 Na^++K^+-ATPase expressed in heart cells, and Schwinger teaches that expression of α1 Na^++K^+-ATPase is significantly reduced in conjunction with heart failure (see, for example, Discussion, pages 2110-2111, in particular left column on 2110, 1st paragraph).

Mohraz provides further confirmation for the teachings of Arystarkhova that the Vg4 antibody binds to an extracellular epitope (see entire document, in particular, Introduction, page 2929).

Given the reference teachings that the Vg4 antibody binds to the extracellular sequence QAATEEEPQNDNL of human α1 Na^++K^+-ATPase, and enzyme involved in heart cell contraction that is down modulated in failing heart tissue, and further given that humanized antibodies for in vivo diagnostic use, it would have been obvious to one of ordinary skill in the art to prepare humanized Vg4 antibodies for the purpose of monitoring heart function in vivo. One of ordinary skill in the art would have been motivated to do so given that, as was well known to one of ordinary skill in the art as of applicant's earliest filing date, heart disease was (is) the most frequent cause of death in the industrialized world and thus in vivo monitoring of heart function is highly desirable. Moreover, and as was well known to the ordinary artisan as of applicant's earliest filing date, the decreased immunogenicity associated with antibody humanization leads to greater serum half life, which is beneficial because it reduces cost and the necessity for frequent patient doctor visits to receive injections. One of ordinary skill in the art would have had reasonable expectation of success in using the humanized Vg4 antibody to monitor α1 Na^++K^+-ATPase expression in vivo given that the epitope for this antibody is extracellular as taught by Arystarkhova and Mohraz.

Therefore, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Moreover, it is noted that claim 7 recites, "the antibody of claim 1, wherein the antibody is administered to a patient...suffering from or susceptible to heart disease and/or muscle contractile disorders," which, given its broadest reasonable interpretation consistent with the instant specification, reads on administration to most of the industrialized world since most of the industrialized world is susceptible to heart disease as it is the most frequent cause of death in the industrialized world. Moreover, the "wherein..." recitation in claim 7 is an intended use of the claimed antibody, and if the prior art structure is capable of performing the intended use, then it meets the claim. In re Casey , 152 USPQ 235 (CCPA 1967); In re Otto, 136 USPQ 458, 459 (CCPA 1963).

21. No claim is allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary Skelding whose telephone number is 571-272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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